UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/259,658	02/26/1999	JOHN COLYER	04256/79245	5554

29933 7590 08/05/2004

PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/259,658	COLYER ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *17-18,21-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *17-18, 21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 17-18,21-40 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2004 has been entered.

Rejections Withdrawn

2. The rejections previously made of record under 35 USC 112, first and second paragraph have been obviated through cancellation and amendment of claims.

Claim Objections

3. New Claims 39 and 40 depend from claims 22 and 23, respectively and are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims set forth a species (proteolysis) of invention that is not encompassed in either of claims 22-23, with respect to "covalent modification"and therefore broaden the scope of claim 22 and 23; claims 39 and 40 are therefore not further limiting of the claims from which they depend.

Claim Rejections - 35 USC § 112

4. Claims 17, 24 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39 and 40 recite the term "proteolysis", this term lacks antecedent basis in claims 22 and 23 from which claims 39 and 40 depend.

Claim 17 is directed to a polypeptide pair that can be, or is not covalently modified through the recitation of "and the reversal of these covalent modifications". This phrase is a conditional phrase, based upon a reversal act, but if the covalent modification that is "required for said association" is reversed, then the polypeptide pair may not be "bound to" each other. The claims recite a contradictory combination of claim limitations that is not internally consistent with what is being claimed. How can both conditions be true at the same time, specifically, a complex formed from the first and second polypeptides ONLY when one of them is covalently modified, as well as being a complex which is NOT covalently modified. The combination of claim limitations is confusing as to what is actually present or absent from the claimed pair is not clearly set forth in the claim.

Claims 24 and 27 should recite ---- further comprising a radioactively or fluroescently labeled polypeptides--- or ------wherein the measuring is through a radioactive or fluorescent label on the first or second polypeptide----; or an equivalent phrase. No radioactive or fluorescent labels are recited or provided in claims 22 or 23. Isn't the "modification" a type of label when a change in molecular mass is measured; claims 24 and 27 are not further limiting of claims 22-23 through the broad recitation of any type of label, when the "modification" set forth in the independent claims are a type of label that permits the detection or measuring of the modification through molecular mass measurements (see claims 31-32, which depend from

claims 22-23). Clarification of the type of label, and distinguishing the "modification" from the presence of an additional label would define claims 24 and 27 as being further limiting of claims 22 and 23.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Fitzpatrick et al (US Pat. 5,710,009).

Fitzpatrick et al disclose and claim a composition that comprises:

an immobilized complex (see claim 19) that comprises the combination of first and second polypeptides, specifically a peptide "reland" (col. 5, lines 4-6, line 22) together with its receptor (see col. 5, lines 54-60).

The reference anticipates the instantly claimed complex that comprises first and second polypeptides that does not comprise a covalent modification based upon the fact that it is not a required component of the instantly claimed polypeptide pair through the recitation of the phrase

"and the reversal of these covalent modifications" which defines the scope of the claimed invention to not require the presence of the covalent modification.

8. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Hochstrasser et al (US Pat. 5,565,352).

Hochstrasser et al disclose a composition that comprises:

an immobilized complex (see Figure 6a), the complex comprising the combination of first and second polypeptides (ubiquitin-oligopeptide covalent conjugate(see col. 1, lines 23-25, and lines 26-45). immobilized on a solid immunoblot surface (see Figures 6a and 6b) , immunoreacted with an anti-ubiquitin antibody polypeptide; also see col. 6, lines 63-67 and col. 7, lines 1-16; Example 4, col. 40, lines 14-56).

Figure 6b shows the combination of polypeptide substrate that has been ubiquintinated with a covalent bond to a ubiquintin polypeptide (see complex formed between "I" and "II" which is subsequently combined with an additional polypeptide "Doa4" in step "IV", the association of which would not take place without the covalent modification of one of the polypeptides with ubiquitin. The product of the Doa4/polypeptide complex is deubiquitin polypeptides ("peptides").

The reference anticipates the instantly claimed complex that comprises first and second polypeptides that comprises a covalent modification, as well as a complex that does not require a covalent modification of one of the polypeptides (ubiquitin/antibody complex).

9. Claims 18, 21-26,31, 34-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Hochstrasser et al (US Pat. 5,565,352).

(Instant claim 18, 21-23,34-40) Hochstrasser et al disclose the instantly claimed method of detecting or monitoring the activity of a modifying agent in the presence of candidate compound; a method of detecting a modifying enzyme on a modifying enzyme that comprises the steps of:

Providing first immobilized (col. 29, lines 40-44; E2 enzyme or deubiquination enzyme and/ or ubiquitin, see col. 1, lines 22-25; col. 33, lines 53-59; first antibody affixed to a solid support (col. 4, lines 34-35; col. 32, lines 56-57) ; or "enzyme coupled to a solid support (see col. 26, lines 66-67 and col. 27, lines 1-5); or affixed to solid support (see col. 29, lines 30-43 and col. 29, lines 5-14); col. 33, line 16 "attached to solid support") and second (short lived eukaryotic protein; a type of polypeptide, col. 1, lines 22-25 and col. 1, lines 45-60) polypeptides,

wherein at least one of the polypeptides is susceptible to modification (deubiquination (col. 1, lines 45-47; col. 7, lines 9-16); or ubiquitination, col. 33, lines 55-65 " E2 modifying enzymes") and the two polypeptides are capable of binding to each other (see col. 14, line 7) ;

and covalent modification (see col. 33, lines 29-51) of one or both of the polypeptides by the modifying agent (ubiquitination is a covalent modification "E2 enzymes, col. 33, lines 55-65 and col. 34, lines 3-8; or the modification may be glycoylation or prenylation (see col. 26, lines 27-33) or deubiquination), in the presence of a modifying group substrate (see col. 29, lines 13-15; figure 6b) results in modulation of the binding of the polypeptides to each other (see Figure 6b, binding is modified to comprise an additional covalent modification, or release of a polypeptide; Figure 6b shows the combination of polypeptide substrate that has been ubiquintinated with a covalent bond to a ubiquintin polypeptide (see complex formed between "I" and "II" which is subsequently combined with an additional polypeptide "Doa4" in step "IV", the association of which would not take place without the covalent modification of one of the polypeptides with ubiquitin. The product of the Doa4/polypeptide complex is deubiquitin polypeptides ("peptides")).

Allowing the polypeptides to bind to each other (see at least Figure 6b)

Contacting the polypeptides with a modifying agent (E2 enzyme or deubiquintinating enzyme or agonist or antagonist (see col. 27-28) in the presence of said modifying group substrate (see col. 27, lines 19; forms ubiquitin-oligopeptide covalent conjugate(see col. 1, lines 23-25, and lines 26-45) or removes ubiquitin from the protein ubiquitin conjugate (see col. 14, lines 4-20); introduces or removes glycosylation or prenylation groups (see col. 26, lines 30-34);

Detecting modulation (see col. 28, lines 54-59; col. 28, lines 24-40) of the binding of the polypeptides to determine a reference signal (baseline activity, see col. 27, lines 19-20) modulation (see col. 25, lines 37-50; section IX, col. 25-28)

Contacting the polypeptides with a modifying agent (enzyme that modifies the first and second polypeptide complex) and a candidate modulator (see col. 26, lines 14-42; col. 27, lines 14-57) of the modifying agent; and

Detecting modulation of binding of the polypeptides in the presence of said candidate modulator and comparing the modulation detected (see col. 28, lines 16-67 in the presence of said candidate modulator with the reference signal ("a control" see col. 28, lines 66-67; col. 29, lines 1-20; "baseline", see col. 27, lines 18-27) modulation (see col. 27, lines 14-17; col. 25, lines 37-50; col. 26, lines 13-43).

(Instant claim 24) at least one of the polypeptides is labeled (see col. 28, lines 27-59; col. 32, lines 56-59; col. 29, lines 5-14; labels: col. 32, lines 16-26).

Instant claim 25) wherein the label is fluorescent (enzyme label, luciferase, B-galactosidase (col. 28, lines 56-57 and col. 30, lines 20-21)

(Instant claim 26) wherein the label is radioactive (see col.28, lines 29-33).

(Instant claim 31) measured by monitoring molecular mass ("mass spectrophotometric or NMR" see col. 29, lines 5-14) and/or chromatography, electrophoresis, sedimentation coefficient (see col. 28, lines 24-52).

(Instant claim 34-36) detected by the association of the second binding partner polypeptide with an antibody that binds the binding partner polypeptide, specifically an anti-ubiquitin antibody (see Figure 6a; and col. 37, lines 35-65) or an anti-deubiquitin antibody (see col. 3-4 and col. 29, lines 35-49 and 50-67; col. 30, lines 1-22).

(Instant claim 40) assaying the reversal of the modification (see section XI, col. 33, lines 25-52; col. 35, lines 7-16 (reversal of covalent bond being the removal of ubiquitin from a polypeptide by deubiquitin and the detection of the ubiquitin polypeptide (protein) through immunoblot analysis with an anti-ubiquitin antibody (see col. 37, lines 23-65).

The reference anticipates the instantly claimed invention.

10. Claims 18, 21-33, 36-40 (high throughput; title, "real time" assay) are rejected under 35 U.S.C. 102(e) as being anticipated by Wagner et al (US Pat. 6,475,809, effective filing date July 14,1998).

(Instant claims 18, 21-23,36-40) Wagner et al disclose the instantly claimed method of detecting or monitoring the activity of a modifying agent in the presence of candidate compound; a method of detecting a modifying enzyme on a modifying enzyme that comprises the steps of:

Providing first immobilized and second polypeptides (see col. 7, lines 40-55 "ras-like GTPases", kinases, phosphatases, hydrolases, proteases, proteases; col. 17, lines 35-41 (enzyme/substrate); all claims),

wherein at least one of the polypeptides is susceptible to modification (see Example 7, and col. 17, lines 35-57) and the two polypeptides are capable of binding to each other (see claims and Example 7) ;

and covalent modification (see col. 33, lines 29-51) of one or both of the polypeptides by the modifying agent (see col. 5, lines 51-60; col. 7, lines 40-55), in the presence of a modifying group substrate results in modulation of the binding of the polypeptides to each other (see all claims)

Allowing the polypeptides to bind to each other (see Example 7, and claims; col. 17, lines 22-57)

Contacting the polypeptides with a modifying agent (see Example 7, and claims, col. 18, lines 6-41) in the presence of said modifying group substrate ;

Detecting modulation (see Example 7, and FRET detection methods (two labels, col. 17, lines 47-57) of the binding of the polypeptides to determine a reference signal (baseline activity, see col. 27, lines 19-20) modulation (see col. 25, lines 37-50; section IX, col. 25-28)

Contacting the polypeptides with a modifying agent and a candidate modulator (see Example 7 and col. 17, lines 35-41 and claims) of the modifying agent; and

Detecting modulation of binding of the polypeptides in the presence of said candidate modulator (drug candidate, col. 18, lines 15-19) and comparing the modulation detected in the presence of said candidate modulator modulation (see Example 7 and col. 18, lines 6-23)

(Instant claim 24-25, 27-30) at least one of the polypeptides is labeled ("Fret", more than one label (see cool, 17, lines 47-57, and thus use of a label: Example 7).

(Instant claim 26) wherein the label is radioactive (see col. 22, lines 43-45).

(Instant claim 31-33) measured by monitoring molecular mass ("NMR" see col. 22, Example 3) and (surface plasmons, col. 17, line 55; chemiluminescence's, surface charge sensors)

The reference anticipates the instantly claimed invention.

11. New Claims 22-23, 39-40 (proteolysis species) are rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al (US Pat. 5,962,637,. filing date December 3, 1996).

Shone et al disclose a method of detecting the presence of a modifying enzyme in sample, wherein the enzyme modifies a polypeptide covalently, and the enzyme is botulism or tetanus toxin. The method comprises the steps of:

Providing a polypeptide pair, a first polypeptide and a binding partner (see Shone et al, claim 1), the first polypeptide is a substrate polypeptide and the binding partner is an antibody capable of binding the substrate with a covalent modification with the enzyme and is labeled with an enzyme;

providing and immobilizing the first polypeptide to a physical support (see Shone et al claim 1, attached to solid support, the immobilized polypeptide is labeled with the detectably labeled antibody to form a detectable complex upon covalent modification with the enzyme in a sample;

contacting the immobilized polypeptide with the second polypeptide (test compound, see Shone et al claims 1, 2 and contacting the immobilized polypeptide with said binding partner polypeptide (see claims 1 and 9, Shone et a1)

Measuring (assaying) the modification (cleavage of substrate) of at least one of the polypeptides by measuring the association of the binding partner polypeptide (antibody binds, see Shone et al The firs polypeptide contains a detectable label.(see Shone et al, claims 6-7, detection of label) . An antibody-binding partner linked to an enzyme is also taught to include a radioactive label (see Shone et al col. 6, lines 37-39) or a fluorescent label (see Shone et al, col. 6, lines 39-42).

The antibody was modified by linking an enzyme to the antibody (see Shone claim 6), or an antibody that binds to the binding partner antibody that is linked to an enzyme (see Shone et al , claim 1.

The assay also comprises the addition of a protease, an enzyme with proteolytic activity (Instant claims 39 and 40) to the test compound which is capable of functioning as an agent (see Shone et al, claim 1, an enzyme that can covalently

modify a polypeptide, such as activate an inactive endopeptidase.)

One polypeptide is immobilized to a support and a second polypeptide bound to the first polypeptide, wherein the two polypeptides are an endopeptidase peptide substrate linked to a carrier protein that is maleimide activated BSA, which is bound to a microtiter plate (see Shone et al col. 15). An additional embodiment disclosed is a polypeptide pair comprising a first lines 45-55. The binding of the two polypeptide one to the other is detectable, and a covalent modification of one of the polypeptides is required for the association of the first polypeptide endopeptidase substrate with the binding partner polypeptide. The assay is carried out over time, thus defining an assay carried out in real time. The reference anticipates the instantly claimed invention.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Beach et al (US Pat. 6,037,136) is cited to show an immobilized polypeptide (col. 11, lines 1-5) that is modified covalently and forms a complex with a second polypeptide, one of the two polypeptides are labeled and assayed in the presence of a modulator (see col. 9, lines 54-67

and col. 10, lines 1-67) , detected with an antibody to the polypeptide (see col. 11, lines 35-51; col. 22, lines 34-38)), detects the reversal of a covalent modification (see col. 12, lines 19-34).

13. Epps et al (US Pat. 6,630,311 is cited to show fluorescence based assays for protein kinases and phosphatases).

14. Hurd et al (5,948,620) is cited to show a reverse two hybrid system employing post-translation signal modification.

15. Lawrence et al (US Pat. 5,416,003; 6,251,621) are cited to show enzyme release reporter assays for measuring proteases.

16. Nash et al (US Pat. 6,714,875) is cited to show a method of screening a combinatorial library for drug discovery.

17. Wagner et al (US Pat. 6,682,942) is cited to show a microdevice for screening biomolecules, the device utilizing immobilized reagents and energy transfer (see paragraphs [146] and [191] and claim 1)

18. Whyte et al (US Pat. 6,261,793) is cited to show an assay method for identifying inhibitors.

19. Williams et al (US Pat. 5,744,313) is cited to show protein domains which bind to tyrosine phosphorylated proteins.

20. WO99/11774 is cited to show assays fore the addition of a post-translational modification and kits that comprise the reagents needed to monitor the addition or removal of the modifications.

21. Wu et al (US Pat. 6,682,898 B2) is cited to show an assay for identifying modulators with an immobilized polypeptide that is phosphorylated receptor peptides (see all claims, figures, see col. 1, lines 50-60 and col. 2, lines 57-60; col. 21, lines 25-27).

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
July 22, 2004

PATRICIA A. DUFFY
PRIMARY EXAMINER